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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/770,639	02/02/2004	Francisco Sanchez-Madrid	27331-501CIP2A	1583

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EXAMINER
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SKELDING, ZACHARY S

ART UNIT	PAPER NUMBER
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1644

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/770,639	<b>Applicant(s)</b> SANCHEZ-MADRID ET AL.	
	<b>Examiner</b> ZACHARY SKELDING	<b>Art Unit</b> 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 10 April 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 56,59,60 and 105-115 is/are pending in the application.
- 4a) Of the above claim(s) 109-115 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 56,59,60 and 105-108 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>7-11-08 and 4-10-09</u> .                                     | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION

1. Applicant's remarks and amendment filed April 10, 2009 are acknowledged.

Claims 56, 105 and 107 have been amended.

Claims 1-55, 57-58 and 61-104 have been canceled.

Claims 109-115 have been added.

Claims 56, 59, 60 and 105-115 are pending.

Claims 56, 59, 60 and 105-108 are under examination wherein the elected species of unwanted immune response to be treated is "rheumatoid arthritis".

New claims 109-115 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 6, 2006.

2. This Office Action is in response to applicant's remarks and amendment filed April 10, 2009.

The previous rejection under 35 USC 112, 1st paragraph has been withdrawn in view of applicant's amendment to the claims.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 56, 59, 60, 105, 107 and 108 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Lubbe et al. (J Autoimmun. 1997 Feb;10(1):87-97) in view of Marzio et al. (Immunopharmacol Immunotoxicol. 1999 Aug;21(3):565-82), McInnes et al. (Nat Med. 1997 Feb;3(2):189-95, hereafter "McInnes 1997") and McInnes et al. (Immunol Today. 1998 Feb;19(2):75-9, hereafter "McInnes 1998"), essentially for the reasons of record as put forth in the Office Action mailed December 10, 2008 as described further below.

Applicant argues the Office Action mailed December 10, 2008 failed to establish a prima facie case of obviousness. Applicant further argues the obviousness rejection was based on an "Impermissible Use of the Obvious to Try Standard." Lastly, applicant argues unexpected

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results render the claimed invention obvious (See Sections a./b., c. and d., respectively of applicant's Remarks filed April 10, 2009).

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed December 10, 2008 as described further below.

### **Prima Facie Case**

Applicant argues the previous Office Action failed to establish a case of prima facie obviousness: "The Examiner has merely asserted that a skilled artisan would have been motivated to combine the above references without identifying where in the references either explicit or implicit motivation can be found to support the rejection... The desirability of the combination is not suggested in any of the references cited by examiner. Accordingly, the Office Action has also failed to establish a *prima facie* case of obviousness because the cited references do not provide a reasonable rationale to combine or modify the teachings of the references to arrive at the present invention. The rationale set forth by the examiner simplifies the facts and forces a wrong conclusion." (see 1st and 2<sup>nd</sup> paragraphs of page 7 Remarks).

Applicant's arguments have been considered, but have not been found convincing.

The examiner directs applicant's attention to pages 6-8 of the previous Office Action which put forth a rejection under 35 U.S.C. § 103 where the reference teachings were put forth with citations to the relevant sections followed by a reasoned conclusion as to why one of ordinary skill in the art would have been motivated to combine them to arrive at the claimed invention.

The reasoned conclusion of the previous Office Action discussing the motivation of one of ordinary skill in the art to combine the reference teachings is reproduced below:

"Given the reference teachings, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made that depleting anti-CD69 antibodies would be excellent alternative to depleting anti-CD4 antibodies for the treatment of rheumatoid arthritis. In particular, it would have been obvious to one of ordinary skill in the art that depleting anti-CD69 antibodies would address many of the problems known in the art of treating rheumatoid arthritis with depleting anti-CD4 antibodies and would be reasonable expected to ameliorate disease as a consequence.

In particular, one of ordinary skill in the art would have been well aware that depleting anti-CD4 antibodies had not lived up to their early clinical promise for treating rheumatoid arthritis as subsequent clinical trials showed these antibodies preferentially depleted naive peripheral blood T cells rather than depleting the disease causing memory T cells (CD45RO+) localized to the rheumatoid synovium.

However, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have had a reasonable expectation of success in treating rheumatoid arthritis with an anti-T cell antibody which preferentially depletes the memory T cells that induce the production of TNF $\alpha$  in the rheumatoid synovium but does not deplete naive peripheral blood T cells.

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*One of ordinary skill in the art would have been motivated to use an anti-CD69 antibody for this purpose given the teachings of Marzio that CD69 is not expressed on naïve peripheral blood T cells but is expressed "at remarkably high levels in synovial fluid and synovial membrane from chronic rheumatoid arthritis patients," and further given the showing of McInnes #1 that the memory T cell induction of TNF $\alpha$  production by macrophage/monocytes is "almost completely abrogated by addition of anti-CD69 antibody."*

*Moreover, one of ordinary skill in the art would have been motivated to make use of a depleting anti-CD69 antibody to treat rheumatoid arthritis given the teachings of McInnes #2 that "cell-directed therapies that not only inhibit T-cell activation but also deplete T cells from the synovial compartment, or at least interfere with their membrane interactions, will probably be most efficacious." Of course, as would be obvious to one of ordinary skill in the art, the best possible anti-CD69 agent would be one that both inhibits the interaction of CD69 expressing T cells with synovial macrophage thereby inhibiting TNF $\alpha$  production and at the same time triggers the depletion of CD69 expressing T cells."*

(see previous Office Action, page 7, 3<sup>rd</sup> paragraph to page 8, 1st paragraph).

Thus, it is the examiner's position that the previous Office Action provided sufficient motivation to treat rheumatoid arthritis with a depleting anti-CD69 antibody.

#### **"Impermissible Use of the Obvious to Try Standard"**

Applicant argues the examiner is using an impermissible obvious to try standard in the rejection of the present claims..." and that "[t]he Federal Circuit has stressed that an invention is obvious when there is a lack of numerous parameters to vary and the prior art gives specific guidance as to how to reasonably achieve success. Citing the decisions of the U.S. Court of Appeals for the Federal Circuit in *In re O'Farrell*, *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, and *Medichem, S.A. v. Rolabo, S.L.*

Applicant goes on to assert: "Furthermore, even assuming, *arguendo*, that McInnes 1998 does suggest molecules other than IL-15 as possible therapeutic targets, the list of other possible targets would have to be expanded include each of the molecules implicated by McInnes 1998 to be involved in the biological pathway that links IL-15 expression to inflammation in rheumatoid arthritis.

Taken together, the references cited by the examiner, in the least, identify the following molecules to be potentially involved in the pathogenesis of rheumatoid arthritis:

1. CD4;
2. IL-15;
3. the myriad of IL-15 receptors, particularly IL15R $\alpha$ ;
4. TNF- $\alpha$
5. leukocyte function-associated molecule 1 (LFA-1),
6. intercellular adhesion molecule (ICAM-1), and
7. CD69.

Thus, at best, the references relied on by the examiner only provide general guidance to a promising field of experimentation and provide insight to a biological mechanism

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hypothesized to be involved in the inflammation seen in rheumatoid arthritis. Unlike the prior art reference in Pharmastem, which spelled out each step of the procedure in question, the references relied on by the examiner point implicate numerous molecules as potentially involved in pathogenesis of rheumatoid arthritis.”

(Applicant’s Remarks at page 12, 1<sup>st</sup>-3<sup>rd</sup> paragraphs)

Applicant’s argument has been considered but has not be found convincing.

Applicant's argument is not found convincing because the instant case is ***not*** one in which “the prior art gave either ***no indication*** of which parameters were critical or ***no direction*** as to which of many possible choices is likely to be successful,” ***nor*** is it one in which the prior art “gave ***only general guidance*** as to the particular form of the invention or how to achieve it.” *O’Farrell*, 853 F.2d at 903.

As put forth in the “Prima Facie” case section above, the prior art provides sufficient motivation and reasonable expectation of success for one of ordinary skill in the art to treat rheumatoid arthritis with a depleting anti-CD69 antibody.

Moreover, applicant's list of seven possible rheumatoid arthritis targets culled from the teachings of the McInnes 1998 review does not represent a list of equivalent choices with no more than general guidance as to which is likely to be successful.

Rather, as is made clear from the teachings of the prior art, one of ordinary skill in the art would have been attracted to certain candidates and less so to others based on the knowledge in the art.

For example, as put forth in the previous Office Action, Van der Lubbe teaches that while initial clinical trials treating rheumatoid arthritis patients with depleting anti-CD4 antibodies reported a beneficial effect, follow up studies such as their own “revealed no therapeutic effect” which was attributed to, inter alia,

(1) failure of the anti-CD4 antibodies to achieve sufficient concentration in the synovial joints, and

(2) selective depletion of naive CD4<sup>+</sup> T cells over CD45RO<sup>+</sup> memory T cells and activated T cells.

(see Van der Lubbe page 94 column bridging paragraph to the end of page 94 and page 90, right column, 2<sup>nd</sup> paragraph to page 91, right column, 1<sup>st</sup> paragraph).

Thus, while the skilled artisan would not have absolutely ruled out the possibility of using depleting anti-CD4 antibodies to treat rheumatoid arthritis, they would have been concerned with the problems associated with pursuing this strategy. Notably, treating rheumatoid

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arthritis with a T cell depleting anti-CD69 antibody is one obvious solution to these problems.

As to targeting LFA-1 or ICAM-1 compared to CD69, the skilled artisan would know from the cited reference teachings as put forth above that CD69 is ***not expressed*** on naïve peripheral blood T cells ***but is expressed*** at remarkably high levels in synovial fluid and synovial membrane from chronic rheumatoid arthritis patients - features which make it an ***especially*** attractive target compared to, for example CD4.

By contrast, the cited art does not teach if LFA-1 and ICAM-1 have the same or different expression patterns. Moreover, while McInnes 1997 shows that antibodies to all three cell surface proteins - LFA1, ICAM-1 and CD69 - can inhibit T cell induced TNF $\alpha$  synthesis from macrophage/monocytes, the major source of TNF $\alpha$  in the rheumatoid arthritis synovium, the anti-CD69 antibody was consistently superior (see McInnes 1997 page 190, right column, 2<sup>nd</sup> paragraph and Figure 7).

Thus, LFA-1 and ICAM-1 appear to be somewhat inferior targets compared to CD69 based on the teachings of the art.

Lastly, as to targeting IL-15/the IL-15 receptors or TNF $\alpha$ , like CD69 these are also good rheumatoid arthritis targets as is made clear from the teachings of the McInnes 1998 review.

However, “[t]he prior art’s mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed....” *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

### **Unexpected Results**

Applicant argues “...the methods of the present claims are based upon unexpected results that shows that depleting anti-CD69 antibody molecules are effective in an *in vivo* model for unwanted immune response. The specification teaches, unexpectedly from the standpoint of one of ordinary skill in the art at the time the invention was made, that it is important that the CD69 specific antibody be a depletor of CD69+ cells, as opposed to specifically binding to CD69, while not depleting CD69+ cells in an *in vivo* model for unwanted immune response...Such evidence demonstrates the criticality of the recited element – depleting anti-CD69 antibody molecules -- *which is an element that is absent in each an every reference that has ever been cited by the Examiner.*”

(see Remarks page 13, 2<sup>nd</sup> and 3<sup>rd</sup> paragraphs, applicant’s emphasis shown).

Applicant’s argument has been considered but has not be found convincing.

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First, it should be pointed out that the McInnes 1998 review teaches that "T-cell-directed therapies that not only inhibit T-cell activation but also deplete T cells from the synovial compartment, or at least interfere with their membrane interactions, will probably be most efficacious." (see, in particular, sentence bridging pages 77-78). Thus, McInnes 1998 specifically teaches the desirability of depleting T cells from the synovial compartment.

Thus, when the reference teachings are considered in combination one of ordinary skill in the art would have expected to successfully treat rheumatoid arthritis with a T cell depleting anti-CD69 antibody.

Moreover, there is a lack of nexus between the claimed invention, i.e., a method of treating rheumatoid arthritis with a depleting anti-CD69 antibody, and applicant's unexpected finding that *the "2.2" anti-CD69 mAb disclosed in the instant specification* down-modulates CD69 from the T cell surface but does not deplete T cells or treat collagen induced arthritis in a murine model system.

This is because applicant has not presented sufficient objective evidence to establish that the "2.2" anti-CD69 antibody exemplified in the instant specification is representative of all non-depleting anti-CD69 antibodies, be they antibodies that down-modulate CD69, block the ability of CD69 to interact with a ligand without down-modulating CD69, or something else related to CD69 signaling.

For example, McInnes 1997 teaches that a particular "neutralizing" anti-CD69 antibody available from Beckton Dickinson, *is capable* of blocking nearly all T cell induced macrophage/monocytes TNF $\alpha$  production in vitro *without depleting T-cells and presumably without down-modulating CD69 expression of the fixed T cells to which it is bound* (see page 194 column bridging paragraph and Figure 7).

Additionally, particular anti-CD69 antibodies have been shown to induce CD69 dependent pro-inflammatory cytokine production in some settings (see, e.g., Marzio page 572, 1<sup>st</sup> paragraph and the paragraph bridging pages 573-574).

In conclusion, when applicant's arguments, the data in the instant specification and applicant's objective evidence of record are taken as a whole and weighed against the evidence supporting a *prima facie* case of unpatentability, the instant claims, by a preponderance of evidence, remain unpatentable over Van der Lubbe in view of Marzio, McInnes 1997 and McInnes 1998.

See M.P.E.P. § 716.01(d).

5. Claims 105 and 106 stand rejected under 35 U.S.C. 103(a) as unpatentable over Van der Lubbe et al. (J Autoimmun. 1997 Feb;10(1):87-97) in view of Marzio et al. (Immunopharmacol Immunotoxicol. 1999 Aug;21(3):565-82), McInnes et al. (Nat Med. 1997 Feb;3(2):189-95, hereafter "McInnes 1997") and McInnes et al. (Immunol Today. 1998 Feb;19(2):75-9, hereafter "McInnes 1998"),



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as applied to claims 56, 59, 60, 67-69, 105, 107 and 108 above,

and further in view of Christine White (US 20020039557 A1), essentially for the reasons of record as put forth in the Office Action mailed December 10, 2008 as described further below.

Applicant argues the instant claims are not obvious because the teachings of White do not cure the alleged deficiencies of Van der Lubbe, Marzio, McInnes 1997 and McInnes 1998 described in Section 4 above.

Applicant's argument has been considered, but has not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed December 10, 2008 and for the reasons given in Section 4 above.

Thus, the instant claims stand unpatentable over Van der Lubbe in view of Marzio, McInnes 1997, McInnes 1998 and further in view of Christine White.

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Zachary Skelding/  
Examiner, Art Unit 1644

/Ram R. Shukla/  
Supervisory Patent Examiner, Art Unit 1644